REMARKS

Reconsideration of this application in view of the following remarks is respectfully requested. Claims 1, 4 and 17-19 have been amended to recite the amount of polymer based on the weight of total biguanide in the dosage form. Claims 7, 15-18 and 20 have been editorially amended to replace the term "HCl" with "hydrochloride." No new matter has been added. Claims 1-20 are pending in this application and at issue.

Obviousness Rejection

Claims 1-20 stand rejected under 35 U.S.C. 103(a) as obvious over International Publication No. WO 00/28989 ("Lewis") in view of International Publication No. WO 01/32158 ("Piper") and European Patent No. EP 440,462 ("Liu"). Applicants respectfully disagree.

The pending claims recite a multi-layer dosage form for once-a-day dosing that includes (i) a first layer comprising a non-biodegradable inert polymer and a biguanide or a pharmaceutically acceptable salt thereof having a particle size less than 100 microns to achieve pH independent release of the biguanide, and (ii) a second layer comprising an active pharmaceutical ingredient (API) (such as a thiazolidinedione). The non-biodegradable inert polymer in the biguanide layer(s) of the dosage form is present in an amount of at least 35% by weight of biguanide in the dosage form. The multi-layer dosage form provides pH independent prolonged release of biguanide and immediate release of the API resulting in improved glycemic control in diabetic patients.

The combination of references cited by the Examiner do not disclose or suggest the presently claimed dosage forms.

Lewis

The Examiner cites Example 4 of Lewis and contends that the amount of non-biodegradable inert polymer is 138% of the concentration of metformin. Applicants respectfully disagree with the Examiner's calculations. As discussed below, Lewis does not disclose or suggest a formulation for pH independent release of a biguanide and immediate release of thiazolidinedione, in which the non-biodegradable inert polymer is present in the dosage form in an amount of at least 35% by weight of biguanide in the dosage form.

Example 4 discloses two tablets, hereafter referred to as Examples 4a and 4b. These examples contain no more than 20.5 % of a polymer based on the total weight of the biguanide in the tablet.

Lewis - Example 4a

Example 4a of Lewis is a "single-layer" tablet, not a multi-layer dosage form as required by the present claims. Therefore, Example 4a is not relevant to the pending claims. However, for the sake of completeness, the calculation of the percentage by weight of non-biodegradable polymer in this single-layer tablet is provided below.

The term "lactose monohydrate to 650" recited in Example 4a refers to the amount of lactose monohydrate required to bring the total weight of the tablet up to 650 mg after the weight of all the other components is taken into account. In other words, the amount of lactose monohydrate is equal to the difference between (1) 650 mg and (2) the total amount of Compound (I), metformin hydrochloride, Eudragit L100-55, Eudragit RS, silicon dioxide and magnesium stearate.

Therefore, in Example 4a, the amount of lactose monohydrate is 47.65 mg/tablet (i.e., 650 – (500 + 74 + 18.5 + 2.6 + 3.25) mg). The single-layer tablet contains 500 mg metformin hydrochloride, 74 mg Eudragit L100-55 and 18.5 mg Eudragit RS (non-biodegradable polymers).

Accordingly, the amount of non-biodegradable polymer (i.e., Eudragit L100-55 and Eudragit RS) in the single layer tablet of Example 4a is 18.5 % by weight of the metformin hydrochloride (i.e., (74 + 18.5) * 100/500). This is a significantly lower content than in the biguanide-containing layer of the multilayer dosage form of the presently claimed invention.

Moreover, the single-layer tablet of Example 4a will provide prolonged (modified) release of both biguanide and thiazolidinedione, because the non-biodegradable inert polymers and both drugs (biguanide and thiazolidinedione) are present in the same layer. This is in contrast to the dosage forms of the present claims that provide prolonged release of biguanide (as non-biodegradable inert polymer(s) are present only in this layer) and immediate release of the other API, such as thiazolidinedione.

Lewis - Example 4b

Example 4b is a tri-layer tablet. Metformin hydrochloride, a biguanide, is present in Layer B and Layer C. The polymers Eudragit L100-55 and Eudragit RS are present in Layer B but not in Layer C.

The total amount of non-biodegradable polymer (Eudragit L100-55 and Eudragit RS) present in metformin hydrochloride containing layers (Layers B and C) is 95 mg per tablet (i.e., 345 -250 mg). The total amount of metformin hydrochloride in Layers B and C is 500 mg. Accordingly, the amount of non-biodegradable polymer in the metformin hydrochloride containing layers of Example 4b is 19 % by weight of the metformin hydrochloride (i.e., 95 * 100/500). This is a significantly lower content than in the biguanide-containing layer(s) of the multilayer dosage form of the presently claimed invention.

Even if, for the sake of completeness, one were to consider the polyvinyl pyrrolidone present in Layer C (7.5 mg) to be a non-biodegradable inert polymer, the amount of non-biodegradable polymer in the metformin hydrochloride containing layers of Example 4b would be 20.5 % by weight of the metformin hydrochloride (i.e., (95 + 7.5) * 100/500). Again, this is a significantly lower content than in the biguanide-containing layer(s) of the multilayer dosage form of the presently claimed invention.

Moreover, the tri-layer tablet of Example 4b will provide prolonged (modified) release of thiazolidinedione, because the non-biodegradable inert polymer(s) are present in the thiazolidinedione containing layer. This is in contrast to the dosage forms of the present claims that provide immediate release of the API, which may be a thiazolidinedione.

Therefore, Lewis does not disclose or suggest a dosage form for pH independent release of a biguanide and immediate release of thiazolidinedione, in which the biguanide layers include a non-biodegradable inert polymer in an amount of at least 35% by weight of biguanide in the dosage form, as recited in the pending claims.

Additionally, as is acknowledged by the Examiner, Lewis "is silent to the particle size of the granulations and active components." *See* Office Action at page 3. The present claims recite that the particle size of the biguanide is less than 100 microns.

Therefore, Lewis does not disclose or suggest each and every element of the pending claims, and does not, therefore, render the pending claims obvious.

Piper

Piper does not cure the deficiencies of Lewis. The Examiner contends that Piper discloses granules, including metformin particles, that are below 24 microns. Applicants disagree.

The particle size reported in Piper is solely directed to glyburide particles, not metformin particles. *See* page 22, lines 10-15 and page 27, lines 2-30. For example, the Table at page 27 is entitled "Particle Size Data for Glyburide Drug Substance Batches Used in Clinical Program." *See* page 27, lines 5-7 (emphasis added). Although Piper (page 23, line 10) contains the stand alone sentence "[p]referably, 50% of particles are less than 23 μm," (page 23, line 10) one of ordinary skill in the art, upon reading the Piper specification as a whole, would understand that this sentence refers to the preferred particle size of the glyburide particles, and not to the particle size of the metformin particles. Accordingly, Piper does not disclose or suggest dosage forms containing a biguanide having a particle size less than 100 microns, as required by the present claims.

Piper also does not disclose or suggest a dosage form in which the biguanide layers include a non-biodegradable inert polymer for pH independent release in an amount of at least 35% by weight of the biguanide, as recited in the pending claims. In addition, Piper is silent regarding multi-layer dosage forms, as recited in the present claims. Indeed, the only dosage forms exemplified by Piper are single-layer tablets (see Examples 1 and 2 of Piper).

Further, Piper is silent regarding the release profiles of both the metformin and the glyburide. Piper does not disclose or suggest dosage forms that provide prolonged release of biguanide and immediate release of an API such as a thiazolidinedione.

Liu

The Examiner has cited Liu for its disclosure of the viscosity of certain components. Liu, however, does not cure the deficiencies of either Lewis or Piper. Liu is solely directed to an

ibuprofen formulation. Liu is completely silent regarding a biguanide formulation, let alone a biguanide formulation containing a second active agent, such as a thiazolidinedione.

Liu also does not disclose or suggest a dosage form in which a biguanide layer includes a non-biodegradable inert polymer for pH independent release in an amount of at least 35% by weight of biguanide, as recited in the pending claims.

Further, Liu is silent regarding the particle size of the active agent. Liu certainly does not disclose or suggest a dosage form containing a biguanide having a particle size less than 100 microns, as required by the present claims.

Therefore, Lewis, Piper and Liu, when taken alone in combination, fail to disclose or suggest each and every element of the pending claims. Accordingly, the cited references do not render obvious the present claims. Applicants respectfully request, therefore, that the rejection be withdrawn.

Conclusion

In view of the above remarks, it is respectfully requested that the application be reconsidered, and that the pending claims be allowed and the case passed to issue. Accordingly, Applicants respectfully request that the Amendment be entered and considered.

If there are any other issues remaining that the Examiner believes can be resolved through either a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned at the telephone number indicated below.

Dated: May 24, 2010

Respectfully submitted,

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